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AND PATHOGENESIS OF MULTIPLE SCLEROSIS

-USSR-

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FOREWORD

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SOME TIMELY QUESTIONS OF THE CLINICAL COURSE, ETIOLOGY
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[Following is the translation of an article by A. L. Leonovich (Minsk) in *Klinicheskaya Meditsina*, Vol. 38, No. 9, Moscow, 1960, pages 43-47/.

Multiple sclerosis is one of the diseases of man over which many unsolved questions have come to a head, especially with respect to etiology, pathogenesis and treatment. Some of the statistics are striking. For instance, in the USA, Switzerland and North Ireland there are four to eight multiple sclerosis patients per 10,000 inhabitants. It is difficult to ignore the geographic factor here, since multiple sclerosis is observed much more frequently in Northern Europe, Great Britain, North America and the USSR than in South Africa, Japan, China, India, South America and Iraq, i.e. among the peoples living in the region of the equator and in Asia. According to Mareczek, Georgi and Jordan, multiple sclerosis is observed almost twice as frequently in Europe as it was formerly. According to the data of the clinic of nervous diseases of the Belorussian Institute for the Improvement of Physicians, 294 patients with multiple sclerosis have passed through its stationary dispensary during the last nine years, which constituted 5.2% of the total number of patients. Through the polyclinic of the Republic's Psychoneurological Dispensary (Minsk) there passed, from 1944 to 1949, 455 patients with multiple sclerosis, forming 1.6% of the total number of initial visits. M. A. Khazanov and M. M. Korin, analyzing 480 cases of multiple sclerosis, came to the conclusion that this disease territorially belongs chiefly to the swamp regions of the Belorussian SSR and the upper courses of a large number of rivers.

What are the causes of the "increase" in the incidence of multiple sclerosis? Is this percentage increase valid?

These causes, in our opinion, are the following:

- 1) the early diagnosis of multiple sclerosis has improved;
- 2) the presence of difficulties in the differential diagnosis, for we do not have a single generally-accepted

specific diagnostic test for multiple sclerosis; 3) the not infrequent expansion of the clinical limits of multiple sclerosis, for under this heading fall patients suffering from other demyelinating diseases (disseminated encephalomyelitis, para-infectious encephalomyelitis, inoculation-vaccinal encephalomyelitis) or simply diagnostically unclear diseases where there is localization of the affections.

An important first-priority task of clinicians is a maximum contraction of the frame of multiple sclerosis, i.e. a proper and careful differential diagnosis.

This study is based on a careful inspection of 150 patients with multiple sclerosis. In our classification we have been guided principally by the clinical course of the disease and have distinguished the following forms (variants) of multiple sclerosis: 1) initial (including so-called neurotic), to which belong 18% of the patients; 2) typical (remittent) with clear and more protracted improvement (42%); 3) progressive, without remissions (15.4%); 4) stationary (4%); 5) acute (8%); 6) apoplectic form (2%); 7) pseudotabetic (3.3%); 8) radiculoneuritic (1.3%); 9) juvenile (6%).

In 82% of the patients the disease developed gradually; an acute beginning without temperature was observed in 16% of the patients, and with a temperature of up to 39° in only 2%. The initial signs of multiple sclerosis were extremely varied: monosymptomatic and polysymptomatic. The monosymptomatic nature of the disease was characterized by isolated weakness in the extremities, paresthesia, peculiar pains, cerebellar disorders, reduction or sudden loss of sight, temporary double vision, etc. This sort of commencement was noted in 48% of the patients, a polysymptomatic one in 52%.

Among the initial signs of the disease, disorders in the motor areas (feeling of weakness in the extremities, paresis, paralysis) were noted in 50% of the patients, cerebellar disorders (vertigo, unstable gait, etc.) in 21%, pains in various localities in 34%, other disturbances of sensitivity (subjective or objective) in 19%, signs of affection of the cranial-cerebral nerves in 17% (including the optic nerve in 9%, the abductor nerve in 7% and the facial nerve (peripheral paralysis) in 1%), vestibular disorders (hyperreflexion, revealed by caloric and rotatory methods) in 61%, scanned speech in 2%, certain deviations in the upper nervous activity (irritability, heightened excitability, rapid tiring, poor sleep, dimming of memory, etc.) in 36% of the patients.

The subjective disturbances of the sensibility in multiple sclerosis are the most varied and not infrequently are the first signs of the disease. They all amount to different kinds of paresthesia ("deadening" of the extremities, "creeps," the feeling of having a jacket or corset in the region of the trunk, itching, etc.). The paresthesias are usually more pronounced in the arms (hands) and less in the legs; they may also occur in the region of the face.

We have made special examinations of multiple sclerosis patients with the aid of the protective-nictitating technique worked out by I. I. Korotkin. We succeeded almost invariably in discovering various deviations in the state of the higher upper nervous activity in all stages of multiple sclerosis, beginning with the so-called neurotic phase. These changes in the higher upper nervous activity were found to be in a certain proportion to the gravity and duration of the disease.

We have attached great importance in the differential diagnosis of multiple sclerosis to the so-called phenomenon of clinical splitting or dissociation (see table). Here we have paid special attention to an investigation of the optic system of the cochleo-vestibular apparatus, the sensitive sphere and the spinal fluid. As is known, a sharp drop in the keenness of vision is noted in a number of cases when the condition of the back of the eye is normal, or a considerable paleness of the papillae of the optic nerve when the keenness of vision is normal; sometimes when the condition of the back of the eye is normal, one observes a sharp narrowing of the fields of vision, the appearance of scotomata (retrobulbar neuritis). To the syndrome of clinical dissociation we also assign vestibular hyperreflexion and hyporeflexion with full preservation of the cochlear apparatus, spastic paresis of the lower extremities with preservation of all types of sensitivity except vibrational, and also albumin-colloidal dissociation in liquid, when with normal albumin

content the reaction curve with colloidal gold is "paralytic" or close to it. Here may also be assigned the high degree of muscular weakness without disturbance to the deep reflexes and, on the other hand, the presence of pathological reflexes (Babinskiy's, Rossolimo's) without a considerable change in the muscular tonus or, finally, spasticity without pathological reflexes. Attention should also be addressed to the dissociation of the superficial and deep abdominal reflexes (disappearance of the former and preservation of the latter.)

Frequency of the Dissociation Syndrome in Multiple Sclerosis

Dissociation Syndrome	Number of Observations (in %)
In the motor sphere	45%
a) presence of pathological reflexes (pyramidal signs) with normal muscular tonus	20
b) pathologically high tendon reflexes without perceptible paresis of the extremities	25
In the optic system	68
In the cochleo-vestibular apparatus	66
In the sensory sphere	62
In the spinal fluid	38

With regard to the etiology and pathogenesis of multiple sclerosis there are thus far several leading theories: traumatic, allergic, vascular, metabolic, infectious, toxic. We shall dwell here upon our research concerning the "specific" serological reactions, skin-allergy tests and non-specific allergy reactions in multiple sclerosis.

The virus of acute human encephalomyelitis identified by M. S. Margulis, V. D. Solov'yev and A. K. Shubladze in 1942 is neutralized in 50% of the cases by the serum of patients with multiple sclerosis. This is also confirmed by our data (in 33 out of 65 patients).

We did not succeed in establishing any dependence between the positive results of neutralization, the oldness or the gravity of the disease. However, in all the patients who had been treated in the past with Margulis-Shubladze vaccine the result of the neutralization reaction

proved positive. One is also struck by the fact that in investigating the neutralization reaction in its dynamics we have in most cases obtained positive results immediately after treatment with the Margulis-Shubladze vaccine (before treatment they were negative). The latter data have evidently affected the total number of positive reactions of neutralization of the virus with the serums of patients with multiple sclerosis.

The skin-allergy test with the Margulis-Shubladze vaccine may have a certain accessory diagnostic significance. According to our clinical data, this subcutaneous test was positive in 53.1% of the multiple sclerosis cases (out of the 111 examined). In certain inflammatory diseases of the nervous system this test gave a positive result in 7.5% of the cases, which we did not succeed in finding in degenerative diseases of the nervous system. The results of the positive tests in multiple sclerosis cases were evidently affected by repeated courses of vaccine therapy, since the skin-allergy test was sometimes made on treated patients. In all 23 patients who had previously received vaccine therapy the subcutaneous test proved positive.

We have tried to ascertain the state of other non-specific allergic reactions in multiple sclerosis. For this purpose, the following methods were used: investigation of the albuminous fractions in the blood serum by the refractometric method and the method of electrophoresis on chromatographic paper, the Weltman and Bukhshtab-Yasinovskiy tests, study of the calcium and magnesium ratio in the blood serum, determination of the total amount of eosinophiles in the peripheral blood, and hyaluronidase.

Both the refractometric method and the method of electrophoresis on chromatographic paper in diffuse sclerosis cases revealed a preponderance of globulin and consequently a reduction in the albumin-globulin index (50.4%). In a majority of the patients a clear preponderance of α_1 (94.5%) and α_2 (62.9%) globulin was noted on account of the lowering of the globulin level (73.1%). In two thirds of the cases examined changes were found: in the Bukhshtab-Yasinovskiy tests (in 33 out of 55 patients a pronounced lowering of the leucocyte level below 10% was noted), and shifts in the Weltman coagulation test; in half the patients disturbances were noted in the calcium/magnesium ratio toward a reduction in the calcium content and an increase in the amount of magnesium (in 16 out of 35 patients). The lowering of the calcium level below 10 mg% and the raising of the magnesium

content above 2.5 mg% were considered by us as one of the indices of the allergic condition of the organism. In most of the patients the drop in the calcium level and the rise in the magnesium content coincided with the period of clinical aggravation of the disease (impairment of the general condition, appearance of new symptoms.)

In half of the patients a pronounced increase in the amount of eosinophiles was noted in the peripheral blood (total over 190, maximum 900 -- in the Fuchs-Rosenthal chamber) and, in two thirds of the patients, a rise in hyaluronidase from 3.3 to 6.7 g.e. To be sure, with respect to quantity the latter group of patients is still insufficient for definite conclusions.

Thus, as a criterion of the reactive condition of the organism we made use of the results of the determination of the calcium and magnesium content in the blood serum, the ratios of fractions of albumin, etc. Our observations in this respect coincide largely with Perger's data and agree with D. A. Markov's views.

As is known, when yperergic reaction is present, a heightened permeability of the endothelium is often noted. The disturbance of the endothelial barrier may be caused by many actions upon the organism (trauma, chilling, high temperature, fatigue, infections, poisonings, hormonal and other factors). Hence, we consider it proper to make additional tests: the Nesterov and MacClure-Oldrich tests and the formation of ultraviolet erythema.

In the Nesterov test more than half the patients (15 out of 28) showed an acceleration of resolution; in 19, heightened permeability; in the MacClure-Oldrich test, an accelerated resolution of the blister (within 15-40 minutes) was determined in two thirds of the patients (38 out of 47); in ultraviolet erythema a heightened erythemic reaction was observed in 19 out of 29 patients.

Thus, the data cited permit one to assume the presence of vascular-vegetative changes in patients with multiple sclerosis and may serve as an indirect index of possible hyperergic reactions in these patients.

Finally, attention must be addressed in multiple sclerosis to the disturbance of fat and lipoid metabolism, especially to lipolytic and lipotropic factors participating in the process of demyelination. This trend must also embrace questions of human nutrition, the study of certain enzymes, vitamins and micro-elements.

According to our data, the antitoxic function of the liver (according to the Kvik-Pytel' test) was disturbed in 77% of the patients; by the thymol test in 29% The atoxyl-

resistant lipase in patients with multiple sclerosis fluctuated from 15 to 35 ml (35 patients examined). A pronounced rise in the cholesterol level in the blood (above 180 mg%) was noted in 14% of the patients, a drop in 41%. The phosphorus content in the blood serum was lowered in 38% and raised in 8% of the patients, the copper content in 31 and 58%, respectively. It should be noted that the fluctuations of the level of cholesterol, inorganic phosphorus and copper in the serum of patients with multiple sclerosis play no leading role in the disturbance of the metabolism in this category of patients. Nor can we hardly be surprised by the presence of lipolytic substances in the serum, as has already been pointed out by a number of authors (Lafontaine, Lesny, Lumsden).

It remains unclear to what extent these disturbances of the metabolism antecede the processes of demyelination or exist parallel to them. Evidently, in multiple sclerosis one may speak of a neuro-allergic pathogenesis in the sense of the rise of different stages of the patch-formation process itself, but of a polyetiologic nature (Pette, D. A. Markov).

Consequently, there is a question as to the non-specificity of the rise of these patches, and hence also of the process of demyelination.

In a clinically clear diagnosis and systematic investigation of the reactivity in dynamics it is possible to determine a very close prognosis, and sometimes even to predict an aggravation or remission of the disease or establish the chronic progressive course.

Conclusions

1. The maximum narrowing of the framework of differential diagnosis of multiple sclerosis is an important first-priority task for clinicians. In differential diagnosis one must reckon with the phenomenon of "clinical splitting" dissociation. Investigations of the specific and non-specific serological and allergic reactions may also be of relative diagnostic significance.

2. The group of multiple sclerosis ailments appears to us to be etiologically collective. Demyelination in multiple sclerosis may be caused by various factors (albumin molecules of substances, exotoxins and endotoxins of bacteria, "anaphylactogens" -- lipolytic or myelolytic --, etc.), i.e. it is due to the sensitization of the nervous tissue by various agents.

3. In questions of the etiology, pathogenesis and especially the treatment of multiple sclerosis, little con-

sideration has thus far been given to the properties of the macro-organism, which evidently are chiefly instrumental in determining the variants of the clinical picture of the disease. We regard the corresponding changes in the reactivity of the organism (ratio of the albumin fractions, calcium and magnesium level in the blood serum, changes in the level of eosinophiles and hyaluronidase) as the basis of pathogenetic therapy of multiple sclerosis.

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